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FOREWORD

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James E. Cremens 7/24/95
PI - Signature Date

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I. Introduction and Background

Iron deficiency anemia is a very common occurrence in premenopausal women, and is usually attributed to blood loss from menses¹, and not further evaluated. However, in the postmenopausal female, gastrointestinal lesions that account for the iron deficiency are found in approximately 70%²⁻¹¹ of patients. In the premenopausal group of women, **no study** has been performed to look at the incidence of gastrointestinal lesions and their potential relation to the iron deficiency. We propose to evaluate premenopausal women with iron deficiency anemia, with upper and lower endoscopy to document the incidence of gastrointestinal lesions in this population. The same day colonoscopy and upper endoscopy is safe and cost effective.¹²⁻¹³ We also will determine if a relationship exists between symptoms and medication usage (ie. NSAID's), and the incidence of gastrointestinal lesions. In obtaining the small bowel biopsy, we will evaluate for Celiac Sprue as this occurs in 3% of iron deficiency^{14,15}, and screen for this with Anti-endomesial Antibodies.¹⁷⁻¹⁸

An increasing number of women are serving in the military today, the majority of whom are premenopausal. Currently, iron deficiency in premenopausal women is most often assumed to result from menstrual blood loss, leading to empiric treatment with iron supplementation. However, the blood loss may result from an underlying gastrointestinal lesion. The gastrointestinal evaluation of premenopausal women with iron deficiency has never been studied, and the military services present a unique opportunity to study a group of women in whom iron deficiency anemia may have a significant impact on the performance of their duties. Usually the gastrointestinal tract is evaluated only if there are overt gastrointestinal symptoms such as gross bleeding. Minor symptoms such as fatigue, and decreased physical ability are only noted, and typically are not acted upon. However, iron deficiency anemia, fatigue, and decreased physical ability may result in diminished readiness among servicewomen.

Early detection and treatment of gastrointestinal lesions can prevent disability resulting from progression to more severe lesion. Servicewomen today are much more likely to be in a deployment and/or combat position with significant responsibilities and stresses unique to their position. These potential stressors could significantly exacerbate many of the potential gastrointestinal lesions which can cause iron deficiency anemia, ie. peptic diseases. Many of these lesions if found early can be easily treated on an outpatient basis with minimal loss of duty time. However, many of these lesions if allowed to progress without treatment or evaluation could result in complications, ie. overt gastrointestinal bleeding, resulting in significant loss of duty time. In today's military, as servicewomen assume many significant roles, their loss even temporarily, can have a significant impact on readiness. At present no data is available on the relationship of gastrointestinal lesions to iron deficiency anemia in premenopausal women.

II. Objectives to be Met

This study is a prospective evaluation of premenopausal women who are found to have iron deficiency anemia. Women who demonstrate iron deficiency anemia, by a ferritin less than 15 mg/dL, and a hemoglobin less than 12 gm/L (World Health Organization criteria)¹⁶, are eligible to participate. We propose to enroll 100 women volunteers. The potential participants will be identified by recruitment of member institutions within our medical treatment catchment (Medical Support Region 8).

DoD Medical Region 8 Member Institutions for referrals include:

FITZSIMONS ARMY MEDICAL CENTER, AURORA, CO.
EVANS ARMY HOSPITAL, FT. CARSON, CO.
PETERSON AIR FORCE BASE, COLORADO SPRINGS, CO.
AIR FORCE ACADEMY, COLORADO SPRINGS, CO.
IRWIN ARMY HOSPITAL, FT. RILEY, KS.
LEONARDWOOD ARMY HOSPITAL, FT. LEONARDWOOD, MO.
MUNSON ARMY HOSPITAL, FT. LEAVENWORTH, KS.
HILL AIR FORCE BASE, OGDEN, UT.
F.E. WARREN AIR FORCE BASE, CHEYENNE, WY.
OFFUTT AIR FORCE BASE, BELLEVUE, NE.
MINOT AIR FORCE BASE, MINOT, N.D.
ELLSWORTH AIR FORCE BASE, RAPID CITY, S.D.

Recruitment within the sponsors' institution, FAMC, has taken place by performing visits to the clinics supporting this protocol which includes the Gynecology, Hematology, Outpatient Clinic, Adult Primary Care, and the Medicine Clinic. These clinics and services have also been visited within the outlying institutions.

III. Procedural Involvement of Volunteers

Volunteer participants undergo a medical history including: menstrual cycle/flow, gastrointestinal symptoms (both upper and lower GI symptoms), present medications (especially NSAIDs and iron supplements). A physical exam will include an evaluation of cardiopulmonary status and evidence of gastrointestinal pathology. Pre-endoscopy drawn labs include a serum pregnancy test (Beta HCG) and Anti-endomesial Antibody to screen for celiac sprue. The participants are then scheduled for the endoscopic evaluation. They undergo a standard bowel preparation the evening prior with Colyte®. The following morning the participant undergoes a full colonoscopy under conscious sedation. Immediately following the colonoscopy, the participant receives further sedation as needed, and will undergo an upper endoscopy and small bowel biopsy (to evaluate for sprue). Same day upper and lower endoscopies have been shown to be both safe and cost effective. The participant is recovered for 1-2 hours until alert and then will be escorted home by a friend or family member according to standard procedure.

Lesions that will be considered significant include: peptic lesions (ie. ulcers of the esophagus, stomach and duodenum), malignancies, polyps > 1cm, AVMs, and sprue. The history and physical exams will be performed by a gastroenterologist or research nurse.

All endoscopic procedures will be performed by qualified endoscopists in the GI clinic utilizing the CV-100 upper endoscope, and the CV-100 colonoscope. The participants will be monitored during and post procedure by the GI clinic nursing personnel using standard practices.

Any biopsies obtained will be submitted in formalin to the Pathology department for microscopic evaluation. Any lesions or pathology found during the evaluation will be treated appropriately by the endoscopist.

IV. Conclusions to be Drawn

We postulate that:

- 1) some premenopausal women with iron deficiency anemia will have gastrointestinal disease, and
- 2) undetected (occult) gastrointestinal disease may cause significant morbidity and diminished performance.

A finding of a high incidence of gastrointestinal lesions in this subgroup of women, could have a significant impact on how all premenopausal women are evaluated. We believe that incidence of gastrointestinal lesion findings will nearly equate the 70% incidence found in the postmenopausal group.

V. Current Impact and Outcome

After evaluating our present group of referrals the following impressions have been made:

A. To date we have contacted 330 physicians, physicians' assistants, registered nurses, nurse practitioners, and Departmental Heads throughout the eight states that serve as a medical referral base for this institution. Our expenses have included recruitment visit costs and a full-time clinical research coordinator. The coordinator has assisted in the final phase of the study evolution to include: advertisements, patient referral procedures, volunteer medical information questionnaires, procedural guidelines for the study, database analysis development and recruitment.

B. Considering the study initiation date (March 8, 1995) this institution has transitioned from potential to declared BRAC nominee status. We have worked vigorously to encourage support from the physician referral base within the region, not only for this study but to maintain our status as a supporting health care entity for the defense members, for which it serves. This is

coupled with the downsizing of all entities in the military communities throughout the region, which has slowed referrals.

C. During the past 120 days we have developed the tools necessary to have volunteers referred to us from their primary care physician, scheduled for the procedural visit, and returned to duty or their home within two weeks. We have also devised a close liaison between our organizations to allow maximum participation and benefit for the females who clinically meet the inclusion criteria. We have completed one patient, and are evaluating four others.

D. We are encouraged by our network of military providers that we will regain enrollment goals and use their feedback on the preliminary data to assist us in analyzing the outcome before the final report submission to your offices. The clinical significance of this study will result in a potential linking of iron deficiency anemia in the premenopausal female to gastrointestinal disease, an alternate avenue in the diagnosis and treatment of anemia, and may significantly impact the readiness of the military female diagnosed with iron deficiency anemia.

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